REMARKS:

Claims 9-18, and 21-38 are pending. Claims 1-8, 19, and 20 have been withdrawn. Claims 9-18, and 21-37 were previously presented. Claim 38 has been amended to correct dependency as requested by the examiner. Claims 39 and 40 are new and do not add new matter. Support for the new claims may be found at paragraphs [0072] and [0083] of the published specification.

I. 35 USC §112, enablement rejection

Reconsideration is requested of the rejection of claims 9-18 and 21-36 under 35 USC §112, first paragraph, for lack of enablement.

Amended claim 9 is directed to a method of decreasing cell proliferation. The method comprises contacting a eukaryotic cell comprising a wild-type MetAP2 with a composition comprising an isolated polynucleotide. The polynucleotide encodes a variant eukaryotic MetAP2 that lacks aminopeptidase activity, comprises a eukaryotic translation domain, and possesses dominant negative MetAP2 activity. The dominant negative activity of the variant MetAP2 decreases the proliferation of the cell.

To satisfy the enablement requirement, a claimed invention must be enabled by the specification so that a person skilled in the art can make and use the invention without undue experimentation. [1] The Office acknowledges that claim 9 is enabled for *in vitro* use, but contends that claim 9 is not enabled for *in vivo* use in species other than yeast. This is not correct. Each of claims 9-18 and 21-36 are fully enabled by the specification commensurate with their scope.

(a) The specification teaches how to "contact" a cell *in vivo*

Amended Claim 9 is enabled for *in vivo* use in species beyond yeast. Claim 9, as stated above, requires "contacting a eukaryotic cell" with a composition comprising a polynucleotide such that the proliferation of the cell is

[1] *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); MPEP 2164.01

decreased. The specification teaches one of ordinary skill in the art how to contact a cell *in vivo*.

In this context, the specification provides several different **types** of vectors that may be used for contacting a cell *in vivo*, including vectors that *may* be used in gene therapy. The Office, in error, has rejected the claims in their current scope for lack of enablement because it is asserted that the specification isn't enabling for "gene therapy." ***Claim 9 does not encompass gene therapy***. Gene therapy is defined in the art as "a technique for the treatment of genetic disease **in which a gene that is absent or defective** is replaced by a healthy gene."[2] Claim 9 requires that the eukaryotic cell comprises a **wild-type MetAP2**, not an absent or defective MetAP2. Stated another way, claim 9 does not provide a method of replacing a gene that is absent or defective, but rather provides a method of contacting a cell comprising a wholly functional MetAP2 gene with a polynucleotide encoding a variant MetAP2. Importantly, vectors that may be used for gene therapy *may also be used in non-gene therapy applications.*

Furthermore, claim 9 is not directed to the treatment of a genetic disease or any other particular disease for that matter. Rather, the scope of claim 9 is directed to a method of decreasing *cell proliferation*.

Consequently, the specification provides that vectors that may be used for gene therapy may be used to contact cells *in vivo* with a polynucleotide encoding a variant MetAP2, such as in example 3. Other methods may be used, however, and are specifically provided in the specification, including human artificial chromosomes.

Therefore, contrary to the Office's assertion, the specification does teach how to "contact" a cell *in vivo* with a polynucleotide comprising a variant MetAP2, as demonstrated by both the specification and its examples.

(b) The teachings of the specification do not require undue experimentation

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[2] The American Heritage® Stedman's Medical Dictionary. Houghton Mifflin Company. 06 Dec. 2007.

The enablement standard requires that the specification teach one of ordinary skill in the art how to use an invention without undue experimentation. The Federal Circuit has outlined eight factors to be considered when making a determination of whether experimentation is undue.[3] The Office's assertions are focused on a single factor, namely, the level of predictability in the art. Specifically, the Office has outlined two related areas of supposed unpredictability: 1) the extrapolation of *in vitro* results to *in vivo* results, and 2) the efficacy and safety of expressing a gene *in vivo*. Each is addressed in more detail below.

i. extrapolation of in vitro results to in vivo results

The Office asserts that the art is unpredictable with regard to any extrapolation of *in vitro* results to *in vivo* gene transfers. The MPEP, however, provides guidance on when *in vitro* results may be taken as correlating to *in vivo* claimed methods of use. In particular, the MPEP specifically dictates that "[I]f the art recognizes a particular model as "correlating to a specific condition [here, angiogenesis], then it ***should be accepted*** as correlating *unless the examiner has evidence that the model does not correlate*."[4] Applicant has provided evidence that human vascular endothelial cells are an accepted model for *in vivo* angiogenesis. In particular, the previously submitted declaration of Dr. Chang explains:

> *in vitro* studies using Human Vascular Endothelial (HUVE) cells are recognized in the art as a model system for studying cell proliferation, and studies using HUVE cells are recognized in the art as correlating with *in vivo* events.[5]

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[3] The factors include: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*

[4] MPEP §2164.02

[5] Chang declaration, point 2(b)

Additionally, the art at the time the application was filed supports the finding that HUVE cells were an accepted model for *in vivo* angiogensis. For instance, preliminary testing on such now approved drugs as TNP-470 were performed in these cells.[6] Notably, TNP-470 has anti-angiogenic effects that stem from inhibiting ***MetAP2***, further supporting the finding that inhibition of MetAP2 in HUVE cells *in vitro* correlates with *in vivo* inhibition of MetAP2. See, for example, Br J Cancer (1994) 69(2):212-6 and J Pharmacol Toxicol Methods (2000)43(1):15-24.

Furthermore, the Office ***has not*** provided evidence that the HUVE model does not correlate with *in vivo* results, as required by the MPEP. "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented ***must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein***."[7] Furthermore, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement made in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.[8] In the present case, the Office action is devoid of any evidence or reasoning which explains why the Office doubts the truth or accuracy for the correlation of the HUVE model with *in vivo* use. Consequently, the HUVE model should be accepted as correlating, and consequently, enabling for decreasing *in vivo* cell proliferation.

The Office further cites, with regard to the unpredictability of *in vitro* results to *in vivo* application, that the expression of "integrated transgenes" is unpredictable. In support, the Office cites to the Bishop reference (the only

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[6] See Br J Cancer. 1994 Feb;69(2):212-6; J Pharmacol Toxicol Methods. 2000 Jan-Feb;43(1):15-24.
[7] MPEP §2164.04
[8] *In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971)(emphasis added).

reference cited to by the Office for its enablement rejection), which describes the chromosomal integration of foreign DNA. Claim 9 ***does not*** require integration. Indeed, many of the vectors, and in particular, the preferred adenovirus vectors described in the specification, ***do not*** integrate into the host cell's DNA. Therefore, the Office's argument and reference regarding integration is moot.

ii. Unpredictability with regard to efficacy and safety

The Office asserts that the art is unpredictable with regard to the efficacy and safety of *in vivo* expression of transgenes. Patent law, contrary to the Office's contention, is separate and distinct from laws and regulations promulgated by the FDA. In this context, patent laws do not have "efficacy and safety" requirements. As stated by the Federal Circuit in *In re Brana*, the Office

> confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption… 'Testing for the full **safety and effectiveness**… is more properly left to the Food and Drug Administration (FDA). *Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings*.'[9]

Furthermore, the Board of Patent Appeals and Interferences (BPAI), in a similar situation, reversed an examiner's enablement rejection based upon "efficacy and safety." In *Ex parte Forstova*, the method claims of Patent Application No. 08/0667 (the '667 application) were directed to a method of "transferring material into a host cell."[10] The examiner rejected the claims under §112 for lack of enablement. The board ***reversed the rejection***, and held that the "opinion that gene therapy will not be enabled until it is clinically available to humans" is not the correct legal standard, and that, "absent a fact-based statement from the examiner which focuses on the ***claimed subject matter*** instead of gene therapy as a general field," the claims were enabled.

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[9] *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995)
[10] Appeal No. 1998-0667 heard 4/11/2002; 2002 WL 32349992

(c) Possible inoperable embodiments will not invalidate a claim for lack of enablement

The Office's arguments amount to an assertion that possible inoperative methods of *in vivo* contacting equates to a lack of enablement for Claim 9. This is not an accurate interpretation of the law. As stated by the Federal Circuit in *Atlas Power Co. v. E.I. Dupont*, "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled."[11]

Furthermore, Claim 9 requires that "contacting" a cell with a polynucleotide of the invention *decreases the proliferation of the cell*. Therefore, the efficacy of the "contacting" is a limitation of the claim. In *Ex parte Mark*, an examiner rejected a claim for a synthetic mutein formed by mutating a cysteine residue to another amino acid.[12] The examiner rejected the claim for lack of enablement, "reasoning that most of the muteins prepared by applicants' methodology would be inoperative because the removal of the cysteine would disturb proper folding of the molecule."[13] The BPAI ***reversed***, however, because the claim "require[d] that the mutein produced retain the biological activity of the native protein… The fact that a given protein may not be amenable for use in the present invention … *does not militate against a conclusion of enablement*."[14]

Consistent with *Ex parte Mark*, the pending claims inherently are directed to only methods of *in vivo* "contacting" that are capable of decreasing cell proliferation. In this vein, the fact that one or more methods of *in vivo* contacting may not be successful in arriving at the claimed result, i.e., decreasing cell proliferation, does not render the claims non-enabled as asserted by the Office. As stated by the Board in *Ex parte Cole*:

> …[c]laims are addressed to the person of average skill in the particular art. Compliance with 112 must be adjudged from that

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[11] *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984)
[12] 12 USPQ2d 1904 (Bd. Pat. App. & Int'f (1989)
[13] *Id.*
[14] *Id.*

> perspective and not in a vacuum. It is always possible to theorize some combination of circumstances which would render a claimed composition or method inoperative, but the art-skilled would assuredly not choose such a combination."[15]

(d) The scope of a pending claim is not to be limited to the preferred embodiments or specific examples

The Court of Appeals for the Federal Circuit "has cautioned against limiting the claimed invention to preferred embodiments or specific examples in the specification."[16] Here, the Office appears to be doing precisely what the Federal Circuit has cautioned against – attempting to limit the scope of the claims only to specific embodiments or examples. It is inappropriate to attempt to limit the scope of the claims to the disclosed *in vitro* examples.

Contrary to the recitations of the Office, "[T]he enablement requirement is met if the description enables any mode of making and using the invention." *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1071 (Fed. Cir. 2005) (citations omitted). This is particularly important as the Office has acknowledged enablement "for a method of decreasing an eukaryotic cell proliferation *in vitro* comprising expressing a heterologous polynucleotide encoding a variant of a eukaryotic MetAP2."[17] Thus, the Office's repeated focus on extrapolation to *in vivo* use is not fatal to enablement, particularly as neither "gene therapy," "gene transfer," nor "*in vivo* use" are identified as claimed elements. The Office's acknowledgement that the present invention is enabled for certain modes is sufficient.

In view of the fact that the specification teaches a skilled artisan to make and use the invention defined by claim 9, applicants respectfully request withdrawal of the rejection based on §112, first paragraph for lack of enablement.

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[15] *Ex parte Cole*, 223 USPQ 94, 95-96 (Bd. Pat. App. 1983).
[16] See, e.g., *Verizon Servs. Corp. v. Vonage Holdings Corp.*, 2007 U.S. App. LEXIS 22737 (Fed. Cir. 2007); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005) (en banc) (cautioning against importing limitations from the specification into the claims); Texas *Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 805 F.2d 1558, 1563 (Fed. Cir. 1986).
[17] See Office Action mailed 9/7/07, page 2.

Claims 10-18 depend from claim 9 and are sufficiently enabled for the reasons detailed above for claim 9.

Additionally, claim 10 requires that the eukaryotic cell is an endothelial cell. Example 3 of the specification teaches using a dominant negative MetAP2 variant in endothelial cells.[18] Therefore, claim 10 is enabled.

Also, claim 11 requires that the polynucleotide is part of a vector and is operably linked to a promoter. Examples 1 and 2 of the specification teach how to use different vectors and promoters in reference to contacting a eukaryotic cell with a polynucleotide encoding a dominant negative MetAP2 variant. Additionally, Claim 12 requires the vector to be an adenovirus vector, claim 13 requires the promoter to be a CMV promoter, and claim 14 requires both an adenovirus vector and a CMV promoter. Example 2 of the specification teaches an adenovirus vector and a CMV promoter. Indeed, the Office agrees that the specification teaches expressing a polynucleotide encoding a dominant negative MetAP2 variant "using an adenovirus vector and CMV promoter."[19] Therefore, claims 11-14 are enabled.

Claim 15 is limited to four eukaryotic variant MetAP2 amino acid sequences. The sequences are specifically provided in the specification. (See SEQ ID NO: 6, 7, 8, or 16.) Similarly, claim 17 is limited to four translation domain amino acid sequences. The sequences are specifically provided in the specification. (See SEQ ID NO: 1, 2, 3, or 15.) Claim 18 is also limited to four eukaryotic variant MetAP2 polynucleotide sequences. These sequences are also specifically provided in the specification. (See SEQ ID NO: 9, 10, 11, and 18). Therefore, claims 15-18 are enabled.

Claim 21 requires that the variant MetAP2 comprises a eukaryotic translation domain and lacks a functional active site pocket such that the variant MetAP2 lack aminopeptidase activity and possesses dominant negative MetAP2 activity. The crystal structure of MetAP2 was available at the time the application was filed, and therefore, one skilled in the art is enabled to make a variant

[18] See paragraph [0133] of the published application.
[19] Office Action mailed February 12, 2007, at pg. 3

MetAP2 by mutating one or more of the residues in the active site pocket defined in the crystal structure.[20]

Claim 22 requires that the variant MetAP2 comprises a eukaryotic translation domain, lacks the ability to bind fumagillin, and possesses dominant negative MetAP2 activity. The specification provides in paragraph [0048] the amino acids involved in fumagillin binding, and therefore, the specification enables one skilled in the art to make a variant MetAP2 by mutating one or more of these listed residues.

Claim 23 requires that H231 is mutated to abrogate fumagillin binding. H231 is a conserved histidine found in every MetAP2 sequenced to date. Therefore, one of ordinary skill in the art would be able to mutate the conserved histidine to make a variant MetAP2. Consequently, the specification enables claim 23.

Claim 24 requires that the variant MetAP2 comprises a eukaryotic translation domain and lacks the ability to coordinate a cobalt ion such that the variant MetAP2 lack aminopeptidase activity and possesses dominant negative MetAP2 activity. At paragraph [0048] the specification provides the specific amino acids involved in coordinating a cobalt ion, and therefore, the specification enables one skilled in the art to make a variant MetAP2 by mutating one or more of these listed residues.

Claim 25 is directed to a method of decreasing cell proliferation. The method comprises contacting a mammalian cell comprising a wild-type MetAP2 with a composition comprising an isolated polynucleotide. The polynucleotide encodes a variant mammalian MetAP2 that lacks aminopeptidase activity, comprises a mammalian translation domain, and possesses dominant negative MetAP2 activity. The dominant negative activity of the variant mammalian MetAP2 decreases the proliferation of the cell. Claim 25 is enabled for the same reasons detailed above with respect to claim 9. Additionally, claim 25 is limited to a variant mammalian MetAP2. The specification provides the sequences of three

[20] Science. 1998 Nov 13;282(5392):1324-7. "Structure of human methionine aminopeptidase-2 complexed with fumagillin."

different mammalian MetAP2 dominant negative variants, namely a mouse, rat, and human variant.[21] Therefore, claim 21 enables one of ordinary skill in the art to make and use a mammalian dominant negative MetAP2. Additionally, claims 26 –36 depend on claim 25, and are enabled for the same reasons detailed above.

New claim 39 is a dependent claim of claim 9, and therefore is enabled for the same reasons as detailed above with respect to claim 9. Additionally, claim 39 requires that the eukaryotic cell is contacted *ex vivo* or *in vivo*. The Office acknowledges that *in vitro* use of claim 9 is enabled.[22] Furthermore, *ex vivo* use is disclosed in paragraph [0083] of the published application, and example 3 discloses contacting a cell in cell culture under conditions analogous to *ex vivo* use of claim 9. Therefore, new claim 39 is enabled.

New claim 40 is a dependent claim of claim 25, and therefore is enabled for the same reasons as detailed above with respect to claim 25. Additionally, claim 40 requires that the mammalian cell is contacted *ex vivo* or *in vivo*. The Office acknowledges that *in vitro* use of claim 9, and consequently claim 25, is enabled.[23] Furthermore, *ex vivo* use is disclosed in paragraph [0083] of the published application, and example 3 discloses contacting a cell in cell culture under conditions analogous to *ex vivo* use of claim 25. Therefore, new claim 40 is enabled.

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[21] SEQ ID NO: 6, 7, 9, 10, 16, and 18
[22] See Office action mailed 9/07/2007, page 2.
[23] See Office action mailed 9/07/2007, page 2.

II. CONCLUSION

In light of the foregoing, applicants request entry of the claim amendments, withdrawal of the claim rejections, and solicit an allowance of the claims. The Examiner is invited to contact the undersigned attorney should any issues remain unresolved.

Respectfully submitted,

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